## REMARKS/ARGUMENTS

Claims 1-16 are active.

Claim 1, as a representative of the invention defines:

> A process for preparing enantiomerically enriched L-α-amino acids or their salts, comprising reacting the corresponding 2-ketocarboxylic acid with an ammonium ion donor in the presence of a whole-cell catalyst comprising a cloned gene encoding a cofactor-dependent amino acid dehydrogenase and a cloned gene encoding glucose dehydrogenase that regenerates the cofactor, at a total input of substrate per reaction volume of ≥ 500 mM, the addition of the substrate being metered such that the stationary concentration of 2-ketocarboxylic acid is less than 500 mM and the external addition of cofactor, based on the total input of substrate, corresponds to < 0.0001 equivalents.

In the Official Action, the Examiner raises a new obviousness rejection citing Galkin, Yamamoto, Hong and Smith. See pages 7-9 of the Official Action. In this rejection, Galkin is alleged to teach a whole cell catalyst in a batch method to produce L-amino acids from ketocarboxylic acids in the presence of ammonium and does not explicitly state that a cofactor is added (see pp. 4652, col. 2, "Production of L and D amino acids"). The Examiner finds that Galkin does not teach a fed-batch process but as performing such a batch-fed process was known from , e.g., Hong, this aspect would have been obvious. The Examiner also acknowledges that Galkin does not teach glucose dehydrogenase but rather formate dehydrogenase for regenerating the cofactor. However, the newly cited Yamamoto patent is relied upon which is alleged to teach that either formate dehydrogenase or glucose dehydrogenase can be used to regenerate NADH from NAD+ (see page 8, 2nd paragraph in the Official Action and paragraph [0046] in Yamamoto) and therefore are equivalent.

It is clear from the rejection that hindsight has been employed to reconstruct the claims from dipartite disclosures that have little to do with each other. To establish that Applicants' claimed process would have been obvious to a person having ordinary skill in the

art, the prior art must reasonably suggest that persons having ordinary skill in the art do what Applicants claims require. Here, the only suggestion to do what Applicants have done is Applicants' own disclosure, i.e. hindsight because the substrates, enzymes and products involved in the process disclosed in Galkin are completely different from the substrates, enzymes and products described in Hong and Yamamoto. In particular, Galkin teaches conversion of α-keto acids with *E. coli* cells with formate dehydrogenase whereas Yamamoto is relevant to a secondary alcohol dehydrogenase. Where, as here, the rejection of the subject matter Applicants claim is based on hindsight, the rejection is improper. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Even though it is acknowledged in the Action that Galkin nor any of the other citations in the rejection teach "a total input of substrate per reaction volume of ≥ 500 mM, the addition of the substrate being metered such that the stationary concentration of 2-ketocarboxylic acid is less than 500 mM" in Claim 1, that is deemed to be obvious based on some unsupported theory of optimization. The examiner's statements in this regard are merely unsupported allegations that are not based on objective evidence or acceptable scientific reasoning. See *In re Lee,* 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (" 'The factual inquiry whether to combine references must be thorough and searching.'...It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with.").

Further there are no teachings in the cited art that the substrate input should be more than 500 mM as claimed nor that this is a variable requiring optimization to the levels as claimed. The Examiner cannot properly conclude that those limitations would have been obvious. See, .e.g., *In re Antonie*, 559 F.2d 618, 195 USPQ 6, 8-9 (CCPA 1977) (exceptions to rule that optimization of a result-effective variable is obvious, such as where the results of

optimizing the variable are unexpectedly good or where the variable was not recognized to be result effective). See also *Ex parte Whalen*, 89 USPQ2d 1078 (Bd. Pat. App. & Int. 2008).

Indeed, contrary to the Examiner's contention, Galkin itself teaches away from those claim limitations. See MPEP § 2141.02 (prior art must be considered in its entirety, including disclosures that teach away from the claims). This is so because the only example in Galkin where a substrate input of more than 500mM is used (Table 2, pyruvate 0.6M) resulted in a significant drop in efficiency (yield 75%) as compared to those examples where lower levels of the same substrate were used (yield = 95% for pyruvate = 0.2M and yield = 92% for pyruvate = 0.4M). Therefore, a person of skill in the art necessarily would take from Galkin's teaching that increasing the substrate concentration more than 0.4 M to be deleterious to the overall reaction. Therefore, even if the teachings of Galkin, Hong and Yamamoto were combined as suggested by the Examiner, a person of skill in the art would not have been motivated to combine the features to arrive at the present invention as – in contrast to the requirements of present claim 1 – Galkin would have provided clear teachings to use substrate inputs of less than 0.4M.

Further and with respect to the Examiner's contention that that formate dehydrogenase and glucose dehydrogenase are functional equivalents relying exclusively on Yamamoto in this regard, this position like so many in the rejection is simply unsubstantiated. Indeed, all that Yamamoto teaches is that each of those enzymes may be useful for regenerating NADH (see [0046] of Yamamoto) but nowhere in this paragraph nor anywhere else in Yamamoto's disclosure is there any statement that they are equivalent, particularly in a process for preparing enantiomerically enriched L-α-amino acids or their salts as claimed. A person of skill in the art starting from Galkin et al. would not have been motivated to modify the process disclosed therein at all, because the system disclosed is already a very complex system and without any indication of a chance to improve this system a person of

skill would not have ventured to change that process with a reasonable expectation of success. See also, *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd,* 533 F.3d 1353, 87 U.S.P.Q.2D 1452 (Fed. Cir. 2008): "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."

In view of the above-discussion, Applicants ask the Examiner to reconsider and withdraw the rejection.

In view of the above, Applicants request withdrawal of this ground of rejection.

The provisional rejection citing co-pending application 12/205,371 and the rejection citing 7,217,544, each in view of Hong, are not sustainable as neither set of claims describes the inclusion of glucose dehydrogenase in the process that also requires a total input of substrate per reaction volume of ≥ 500 mM, the addition of the substrate being metered such that the stationary concentration of 2-ketocarboxylic acid is less than 500 mM. For the reasons stated above in regard to the 103 rejection, Hong's disclosure is insufficient to render obvious the claims as the alleged functional equivalence of the enzymes in question is unsupported and indeed fails to establish a reasonable expectation of success. Accordingly, the burden of establishing *prima facie* obviousness in these two rejections has not been met.

Withdrawal of both rejection is requested.

A Notice of Allowance is also requested.

Respectfully submitted,

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